

HIV and venous thrombotic events

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Summary

HIV has been widely recognised as a prothrombotic condition, with the first case reports having appeared more than 20 years ago. However, surprisingly little evidence is available regarding the mechanisms by which this disease leads to thrombosis. There is little doubt that the relationship is both multifactorial and complex. This review aims to look at the available data and provide a concise summary of the present level of knowledge.

HIV infection has been recognised as a prothrombotic condition, with the first isolated case reports of the association between venous thrombo-embolism (VTE) and HIV infection starting to appear in the late 1980s. This association has now been conclusively proven by a large number of studies, the first significant study by Hassell *et al.*¹ in 1994 reporting an incidence of deep-vein thrombosis (DVT) of 18% in a group of 60 HIV-positive patients. A systematic review published in 2005 found an incidence ranging from 0.19% to 18%.² This incidence is well in excess of what one would expect in a non-infected population, where the average risk of developing DVT is reported to be approximately 5/10 000.³

As a consequence of the high number of HIV-infected individuals in southern Africa (in South Africa it is estimated that there are 5.7 million HIV-positive individuals out of a total population of 44 million⁴), HIV-related thrombosis is an important aspect of this disease. In an audit performed at Johannesburg Hospital, 84% of patients who presented with DVT were found to be HIV positive.⁵

The severity of the HIV infection appears to be of significance in this association, several studies having confirmed that there is a higher incidence of venous thrombosis in patients with low CD4 counts, while the risk rises still further when individuals have confirmed AIDS. Laing *et al.*⁶ found that the incidence of DVT was twice as high in patients with AIDS as in those with HIV infection without manifestations of AIDS. Ahonkai *et al.*⁷ reported a significant risk for patients with a CD4 count less than 500 cells/ μ l, and several other studies have confirmed the correlation between CD4 count and the risk of developing VTE.^{8,9}

The reason for the relationship of HIV infection with thrombosis has not yet been conclusively elucidated, but it appears to be multimodal, with all three limbs of Virchow's triad being involved. However, despite the extent of the HIV pandemic, surprisingly little work has been done on defining

the exact mechanisms by which this phenomenon occurs.

The aim of this review is to provide an overview of what is currently known about the risks and mechanisms of VTE in HIV-infected individuals. In addition, there has been speculation surrounding the role of protease inhibitors in the development of VTE, as well as other medications making up the standard highly active antiretroviral therapy (HAART) regimens. Several early retrospective studies showed a mild increase in risk; however, in a recent publication Crum-Cianflone *et al.*¹⁰ could prove no such association. This finding echoes those of several smaller, more poorly designed studies.

The role of pro- and antithrombotic proteins

Both pro- (which are increased in concentration) and anti-coagulant proteins (which are reduced in concentration) in blood have been studied extensively to ascertain which are affected by the HIV infection. Very few have been found to be significant on their own. It is likely that a combination of factors is responsible for tilting the scale in favour of the pro-coagulant state in individuals infected by HIV.

Protein S

Protein S is a coagulation inhibitor which is synthesised in the liver and is usually found bound to membrane phospholipids; 60% is in an inactive form, and 40% is found circulating in an unbound form. The role of protein S is as a co-factor for activated protein C in the degradation of factors Va and VIIIa. The risk of hereditary protein S deficiency has been estimated at 1/30 000.¹¹ The work of Lafeuillade *et al.*¹² has been invaluable in demonstrating the link between HIV and protein S levels. There is a significant presence of anti-protein S antibodies in the blood of patients with HIV infection, leading to significantly lowered protein S activity. Stahl *et al.*¹¹ confirmed these findings and observed that there was no correlation between the CD4 count and serum levels of protein S, while Sorice *et al.*¹³ found a statistically significant correlation. It is currently widely accepted that a protein S deficiency is a significant contributor to the procoagulant nature of HIV disease.

Protein C

The relationship between protein C and HIV infection is not quite as clearly delineated as that of protein S. In a study of 109 patients infected with HIV, Lijfering *et al.*⁸ could only demonstrate a protein C deficiency in 9% of their cohort. Feffer *et al.*¹⁴ demonstrated a mean protein C level that was

decreased but still within the normal limits. It is thought that protein C is consumed during HIV infection due to its anti-inflammatory role, but a clear relationship between the two has not been adequately defined. Interestingly, there have been no reports of factor V Leiden mutations (a protein C-resistant state) in HIV-positive patients leading to thrombotic events.

Heparin co-factor II

Heparin co-factor II (HCII) inhibits thrombin. Low levels of HCII have been shown to increase the risk of thrombosis in non-HIV-infected individuals. In 1993 Toulon *et al.*¹⁵ found a clear correlation between HCII levels and CD4 counts in patients infected with HIV. Patients who had AIDS had even lower mean HCII levels. However, no paper has shown a direct correlation between the low HCII levels in HIV-positive patients and the prothrombotic state, and it is uncertain to what extent low HCII levels contribute to this.

Antithrombin deficiency

Although there is no direct evidence of HIV infection leading to antithrombin deficiency, it is suspected that antithrombin deficiency is secondary to liver and kidney disorders caused by HIV disease. HIV-induced malignancies may also cause antithrombin deficiency, although firm evidence is lacking at present.

The antiphospholipid syndrome (APS)

The APS has long been associated with thrombosis. Antiphospholipids are procoagulants that prolong the aPTT test. Although a diverse collection of antibodies fall under the APS moniker, the ones most commonly found in patients infected by HIV are the anticardiolipin antibodies, ranging in frequency between 7% and 17.8%,¹⁶⁻¹⁸ and anti- β_2 -glycoprotein I (6 - 33.3%). In systemic lupus erythematosus (SLE) the APS is associated with thrombotic complications. However, Palomo *et al.*¹⁸ and Galrao *et al.*¹⁷ both failed to show a statistical correlation between the APS and thrombotic complications in HIV. Galrao's paper is the only one that looked for a correlation between CD4 count and antiphospholipid antibodies (APLAs) – finding none.

Cytomegalovirus (CMV)

CMV is a well-established cause of thrombosis. There are three proposed mechanisms by which CMV is thought to cause thrombosis.¹⁹ The first hypothesis suggests that CMV leads to a thrombotic micro-angiopathy by changing the nature of the endothelium from a anticoagulant to a procoagulant state. This is accomplished by inducing tissue factor in endothelial cells. The second hypothesis involves induction of the APS, but this has to a large extent been discounted. The final hypothesis involves impaired fibrinolysis due to raised haemostatic parameters such as von Willebrand factor (VWF). However, there is little evidence to support this. Nonetheless, there is a strong association between concomitant HIV and CMV infections and VTE.

Microparticles

The term 'microparticles' refers to small cellular remnants that circulate in the plasma.^{2,20} They are thought to originate from endothelial cells, as well as platelets and CD4 lymphocytes. They are best described as small non-nucleated phospholipid vesicles that express binding sites for factor V.

Endothelial microparticles are also thought to contain VWF, which leads to platelet aggregation and therefore the risk of thrombosis. Elevated levels of microparticles have been identified in HIV-positive patients,²¹ but there is no clear evidence that this causes a rise in the risk of VTE.

HIV and platelets

Thrombocytopenia is a common finding in patients with HIV infection. The presence of raised levels of VWF in these patients can promote platelet aggregation and adhesion.^{14,22} VWF can also lead to raised levels of tissue plasminogen activator and its inhibitor. Bain²³ showed that p-selectin is a marker of platelet activation, and in a 1998 study Holme *et al.*²⁴ showed that HIV-infected patients have significantly raised levels of activated platelets, as evidenced by these platelets having increased levels of microvesicles, as well as p-selectin levels, CD63 and aminophospholipids. These levels and subsequently the levels of activated platelets were shown to be reduced once antiretroviral therapy was introduced. In a more recent study, von Hentig *et al.*²⁵ confirmed that the addition of protease inhibitors to HAART regimens did not lead to increased procoagulatory capacity as assessed by platelet function.

The vessel wall

HIV infection activates the endothelium, leading to endothelial dysfunction and thrombosis. Endothelial cells play an important role in haemostasis, being involved in the procoagulant, anticoagulant and fibrinolytic processes.²⁶ It is now a well-established fact that there is a primary infection of endothelial cells by the HIV virus, with the first report appearing in 1989.²⁷ Multiple studies have also reported the role of HIV in causing endothelial dysfunction.²⁸ Joshi *et al.*²⁹ have described significant inflammation in coronary vessels of children infected with HIV. This inflammation leads to a procoagulant state, various markers of which have been described. The most commonly available surrogates of endothelial function available include VWF, soluble thrombomodulin and soluble E-selectin.³⁰ Raised levels of these markers in the blood indicate that the endothelium has been activated. These substances then lead to alterations in the coagulation cascade, predisposing to thrombosis. Raised levels of all three substances are found in HIV infection. VWF has been shown to be raised up to 60% in patients with HIV, and its levels correspond inversely with CD4 levels.³¹ VWF and soluble thrombomodulin have been shown to be inversely proportional to p24 antigen. Ross *et al.*³² recently compared endothelial activation markers in antiretroviral-naive patients with those on treatment. They specifically looked at VWF, as well as soluble intercellular adhesion molecules (ICAM) and vascular cell adhesion molecules (VCAM), and found that the endothelial activation markers in patients on therapy are very close to those in healthy individuals, further proving the benefit of treating patients with HAART. Torriani *et al.*³³ have also published a paper showing the rapid improvement in endothelial cell function once HAART has commenced. There is therefore strong evidence that uncontrolled viraemia is a direct cause of endothelial dysfunction.

Impaired flow

Although Kaposi's sarcoma and lymphoma are the only HIV-related tumours that have been proven to be procoagulant,^{9,34}

a large number of HIV-related tumours have been shown to affect blood flow by direct compression of vessels, as well as direct infiltration of the vessel wall.

Prophylaxis and therapy for HIV-related thromboses

There is no available evidence evaluating thromboprophylaxis in HIV-infected individuals. In addition, the guidelines for treatment of thrombosis in HIV-infected individuals are silent on this subject. It is remarkable that in the 2008 ACCP guidelines on antithrombotic and thrombolytic therapy³⁵ the words HIV, AIDS and CD4 do not appear once. This means that clinicians are left to make their own decisions with regard to prophylaxis and therapy of HIV-related thromboses. However, in dealing with such a chronic disease, which is clearly prothrombotic in nature, prophylaxis is warranted in much the same way as it would be for a patient suffering from cancer. Unfractionated or low-molecular-weight heparin is an appropriate prophylactic agent, as the only clearly identified high-risk factor is protein S deficiency.

There is nothing to suggest that anything other than standard treatment protocols for patients with proven VTE should be followed in HIV-infected individuals.

Conclusion

HIV is clearly established as a prothrombotic condition. Although many pathways have been investigated to determine the mechanism, the only strong evidence available appears to be for protein S deficiency. Many other factors appear to play at least some role, and it appears inevitable that the mechanisms underlying thrombosis associated with HIV infection are multimodal. It is likely that new proteins will be candidates for investigation in the future and that there will be far more accurate risk determination systems available to us in order to predict the individual risk of thrombosis. One of the controversies in this field is the question of whether DVT in the patient infected with HIV should be considered an AIDS-defining disease. Our approach is that it should be. This is partly due to the association of thrombosis with a dropping CD4 count, but also to the clinical implications of DVT and the increased need for thromboprophylaxis, which is similar to that in the patient with a malignant disease.

Surprisingly little work has been done in the realm of thrombosis in relation to HIV. As HIV progresses towards becoming a chronic disease rather than a fatal one, this is also likely to change. Importantly, there is no strong evidence to suggest that protease inhibitors lead to an increased risk of thrombosis.

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